REMARKS

Claims 1, 4, 5, 7-11, 14, 15, 17-22, 25, 26, 28 and 29 have been amended herein to more particularly point out and distinctly claim that which the inventors regard as their invention. Claims 7, 8, 17, 18, 28 and 29 have been amended to specify that the substitution is made at a position corresponding to a particular position in the human light or heavy chain variable region, which amendment has support, *inter alia*, at page 11, lines 3-12 of the specification. The other amendments made herein are to clarify the claim language and, as such, are fully supported by the specification and do not add any new matter. Claims 2, 3, 6, 12, 13, 16, 23, 24 and 27 have been withdrawn from consideration as not being drawn to the particular species of gonadotropin releasing hormone (GnRH) elected by Applicants. Applicants understand, however, that if the claims to GnRH are found to be patentable, that the Examiner will proceed to examine the non-elected species and the claims generically. Accordingly, claims 1-31 are currently pending in the application.

Applicants have also, pursuant to the Examiner's suggestion, amended the title of the application to better reflect the claimed subject matter.

1. The Invention

The presently claimed invention relates to engineered immunoglobulins that have one or more complementary determining regions (CDRs) containing an antigenic polypeptide from a protein that plays a role in reproductive function. The immunoglobulin molecules of the invention lack one or more of the cysteine residues that characteristically participate in forming intra-molecular disulfide bonds. In particular, immunglobulin molecules having CDRs with such an antigenic peptide have a substitution with a residue that does not have a sulfhydryl group at a position that in naturally occurring immunoglobulin molecules has a cysteine residue that forms an intramolecular disulfide bond. Although such immunoglobulin molecules may or may not retain the ability to bind a particular antigen, the present inventors have found that such immunoglobulins have an enhanced ability to induce an anti-idiotype reaction, *i.e.*, are better antigens. Accordingly, by inserting into the CDRs of an immunoglobulin, an antigen involved in reproductive function, the engineered immunoglobulins of the invention can be used to induce an immune response against the antigen, thereby disrupting the reproductive process as a contraceptive measure.

2. Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1, 4, 5, 7-11, 14, 15, 17-22, 25, 26, and 28-31 under 35 U.S.C. § 112, second paragraph, as indefinite. In particular, the Examiner finds unclear the recitations "having at least one CDR that has a portion of an antigen of a cell or protein involved in reproductive function"; and "said one or more amino acid substitutions of one or more amino acid residues that do not have a sulfhydryl group at one or more positions corresponding to one or more cysteine residues that form a disulfide bond in said second immunoglobulin"; and the term "identical". As discussed below, Applicants have clarified the claim language by amendment, thereby overcoming the rejection.

Although not conceding that the claims were previously indefinite, Applicants have amended the claims to clarify that the at least one CDR of the recited immunoglobulin molecule has within it an antigenic portion of a protein, such as gonadotropin releasing hormone, that is involved in reproductive function. Although not excluding the possibility that the CDR or immunoglobulin may bind such a protein involved in reproductive function, the claim language specifies that a CDR of the immunoglobulin contains a portion of a reproductive protein wherein the portion is antigenic.

Applicants have further amended the claims to make clear that the recited amino acid substitutions are substitutions at positions that have a residue having a sulfhydryl group (particularly a cysteine residue) and that participate in disulfide bond formation, which residues are substituted with a residue that does not have a sulfyhydryl group and, as such, does not form a disulfide bond. In other words, the claimed molecules have a residue other than cysteine or methionine in place of a sulfhydryl-containing residue (almost invariably cysteine) that would otherwise form an intrachain disulfide bond. The recited amino acid substitution is intended to disrupt at least one intramolecular disulfide bond in the immunoglobulin molecule.

Finally, the claims have been amended so that they do not include the term "identical," thereby rendering this aspect of the rejection moot.

Applicants submit that the amendments and above-made arguments have overcome the Examiner's rejection under Section 112, second paragraph.

3. Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner has rejected claims 1, 4, 5, 7-11, 14, 15, 17-22, 25, 26, and 28-31 under 35 U.S.C. § 112, first paragraph, as not enabled by the specification. In particular, the Examiner alleges that, while the specification enables an "immunogenic composition

regarding an antigen from a molecule involved in reproduction," it does not reasonably enable "a vaccine." The Examiner further indicates that the claims are not enabled because the specification does not provide guidance for the claimed "molecules sufficient to induce an anti-idiotype response" without undue experimentation. The Examiner further indicates that it is unclear how anti-idiotype antibodies against GnRH, which antibodies would have the same biological action as the protein itself, would mediate contraception since GnRH stimulates gonadal growth and function. And, finally, the Examiner finds that glycosylation of the immunoglobulin molecule as well as the recited mutations in the light or heavy chain might have a deleterious effect on the ability of the recited immunoglobulin molecule to bind its antigen. Applicants respectfully traverse the rejection.

First, although not conceding that the specification does not enable a vaccine for contraceptive use, Applicants have amended all the pending claims to delete the term "vaccine" such that the claims recite a "composition" comprising the recited immunoglobulin molecule. Applicants submit that, by following the Examiner's suggestion, they have overcome this aspect of the rejection.

With regard to the remaining aspects of the rejection, Applicants highlight that the purpose of the claimed immunoglobulin molecules is not passive immunotherapy--these molecules are not themselves designed to bind to or mimic the protein involved in reproductive function. The immunoglobulin molecules are designed to be antigens to elicit an endogenous immune response against the particular protein involved in reproductive function (an antigenic portion of which has been inserted into a CDR). The present inventors have found that disrupting the intrachain disulfide bonds improves the antigenicity of the immunoglobulins. Thus, the claimed immunoglobulins that, for example, contain a portion of the GnRH, are to be administered to produce antibodies against GnRH and are not designed to bind or mimic GnRH or any other cellular protein for that matter.

Applicants submit that, having clarified the invention, they have overcome the rejection.

4. Rejection Under 35 U.S.C. § 112, first paragraph, written description

The Examiner has also rejected claims 1, 4, 5, 7-11, 14, 15, 17-22, 25, 26, and 28-31 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to convey to one skilled in the art that, at the time the application was filed, the inventors were in possession of the invention. The Examiner contends that the specification does not describe the structural features of the claimed

molecules that are related to the recited function of inducing an anti-idiotype response. Applicants respectfully traverse the rejection.

The specification and the claims themselves recite that the immunoglobulins of the invention (1) have CDRs containing an antigenic portion of a protein involved in reproductive function; and, critically, (2) have a substitution of at least one residue that participates in intramolecular disulfide bonds with a residue that does not participate in intramolecular disulfide bonds. These two structural features define the claimed immunoglobulins that have enhanced capability of eliciting an immune response. By defining these structural features and reciting them in the claims, Applicants submit that they have complied with the written description requirement and request withdrawal of the rejection.

5. Rejection Under 35 U.S.C. § 102

The Examiner has rejected claims 1, 4, 5, 7-11, 14, 15, 17-22, 25, 26, and 28-31 under 35 U.S.C. § 102 as anticipated by United States Patent No. 4,556,555 issued to Esbenshade ("Esbenshade"). The Examiner indicates that Esbenshade discloses the use of a purified population of polyclonal antibodies against GnRH, which antibodies would be sufficient to induce an immune response, for the sterilization of an animal. Accordingly, the Examiner contends that Esbenshade discloses every element of the claimed invention, thereby anticipating it. Applicants respectfully traverse the rejection.

Esbenshade essentially discloses passive immunotherapy using serum from animals immunized with GnRH, which serum contains antibodies against GnRH, to prevent sexual development of farm animals. The Examiner has provided no evidence (nor is any evident from the face of Esbenshade) that the polyclonal antibodies of Esbenshade that bind GnRH either (1) contain a portion of GnRH within one of CDRs of these antibodies or (2) have a substitution of one of the sulfhydryl containing residues that form a disulfide bond with a residue that does not contain a sulfhydryl group, both of which are required by the claims. Since Esbenshade does not disclose either explicitly or inherently every element of the claimed invention, Esbenshade does not anticipate, nor does it render obvious, any of the claims. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Entry of the amendments and remarks made herein is respectfully requested. Applicants believe that all of the rejections of the claims have been overcome herein and respectfully request early allowance of the pending claims. If any issues remain in connection herewith, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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